



AdvaMedDx

Vital Insights | Transforming Care

## Statements on the Regulation of Laboratory Developed Tests

Current Regulatory Gaps and Perspectives on Oversight of LDTs

### **42 Health care stakeholder organizations say...**

“[T]he undersigned organizations, representing patients, advocates, caregivers and health care professionals, would like to emphasize the important role FDA can and needs to play in the regulation of laboratory developed tests (LDTs).

“Concerns have been raised that FDA involvement in LDT regulation will impede patient access to innovative tests. However, it is important to note that the FDA has a track record of exercising regulatory flexibility to bring new technologies to patients in a timely manner ... The FDA’s draft guidance on LDT oversight also reflects a commitment to flexibility, given the proposal’s risk-based approach to oversight.

“Beyond providing timely access to new products, the FDA can effectively fill current gaps in oversight that have led to uncertainty surrounding the quality of some tests ... the general lack of publicly-available information about many LDTs has raised concerns among many that not enough is known about many tests currently in use.

“As Congress weighs various proposals to reform LDT oversight, we urge lawmakers to recognize that FDA involvement does not mean a threat to patient access. Moreover, patients deserve to have confidence in the results of in vitro diagnostic tests, since such tests inform a variety of treatment decisions. The FDA can provide the assurance that when tests are performed they lead to the proper use of associated treatments, a step that’s necessary to improve the public health.”

Letter to Congress, November 11, 2015;

### **American Society of Clinical Oncology says...**

“Prevailing regulations that apply to LDTs offered for clinical use, namely CLIA, do not assess the safety and effectiveness of LDTs offered by laboratories. Rather, they determine that the laboratory follows generally accepted standards for good laboratory practices.”

September 19, 2014

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### **BlueCross BlueShield Association says...**

“We believe that regulatory oversight will, in a number of ways, encourage the development of new, more accurate, or more efficient diagnostic tests. Presently, payers are filling the regulatory gap by assessing analytic and clinical validity of molecular diagnostic tests as a condition of coverage. While payers will certainly continue to assess clinical utility, regulatory oversight would be a more efficient path to satisfying payer requirements to demonstrate analytic and clinical validity. Moreover, the existence of sound evidence on clinical validity would allow test developers, clinicians, and payers to more efficiently assess the clinical utility of tests and the market to more intelligently drive investment in development. The playing field between diagnostic kits and LDTs would be leveled, as uneven competition between kit manufacturers and laboratories, which is a barrier to development companion diagnostics and targeted therapies, would be diminished.”

Comments to 21st Century Cures White Paper on Laboratory Developed Tests January 5, 2015

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### **Editor-in-Chief of Journal of Molecular Diagnostics says...**

“[T]o suggest that the proposed FDA actions will seriously curb innovation is wildly speculative. Unfortunately, CLIA alone, as currently implemented, may well be inadequate. There are no strong standards in CLIA for validating LDTs, and there is no centralized reporting mechanism by which the public can become aware of either the magnitude of LDT testing, the benefit derived from this testing, or adverse consequences associated with this testing.”

*The Journal of Molecular Diagnostics* November 2014  
Editorial Regulating Laboratory-Developed Tests by Timothy J. O’Leary, MD, PhD, Editor-in-Chief

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### **Former Secretary of Maryland Department of Health and Mental Hygiene says...**

“A patient travels by an ambulance that is regulated, to a hospital that is regulated, for care using medicines that are regulated, administered by nurses and physicians, who are regulated. Yet today, that same patient’s life or death could hinge on whether a single, unregulated diagnostic test result is meaningful. The FDA is right to bring a measured approach to ensuring the quality, safety, and validity of laboratory-developed tests.”

JAMA Editorial January 5, 2015 by Joshua Sharfstein, MD,  
Former Secretary of Maryland Department of Health and Mental Hygiene

### **American Association for Cancer Research says...**

“Implementation of a risk-based framework by the FDA that would provide for evaluation of all high-risk molecular diagnostic tests would balance the need for encouraging innovative medical product development with the need for ensuring patient safety. A focus on high-risk tests would also help channel the FDA’s limited resources toward those products that pose the greatest health risks for patients. Having a predictable and reliable regulatory environment is important for patients and for diagnostic and drug developers, since the success of a targeted therapy is inextricably linked to the successful development of its companion diagnostic test. Therefore, a single regulatory standard for high-risk diagnostic tests is key to ensuring the safety and efficacy of molecular diagnostic tests.”

September 9, 2014

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### **American Cancer Society Cancer Action Network says...**

“Molecular tests, in particular, have become an increasingly integral part of critical treatment decisions about whether or not a particular patient would benefit from a course of therapy. As patients and doctors become more reliant on diagnostic tests to provide this information, it is critical that they are valid and accurate. However, many tests come to market without independent verification of their clinical validity by a government or independent agency. Testing kits should be cleared or approved by the FDA prior to marketing; however, the vast majority of laboratory-developed tests (LDTs) are marketed without such reviews. When the FDA began regulating medical devices, LDTs were relatively simple, low-risk tests. Now, LDTs encompass even the most advanced molecular diagnostics, such as higher risk tests that are essential for safe and effective use of cancer therapeutics or are critical determinants in the treatment of serious, life threatening diseases. With diagnostic testing and targeted therapies on the rise, the stakes are now much higher for cancer patients. LDTs are becoming more numerous, more complex, and have the potential to have a significant impact on health care decisions, and the FDA should provide oversight of LDTs that could pose risk to patients if not fully understood. This should allow the medical community to take full advantage of these new tests.”

Letter to U.S. House of Representatives Energy and Commerce Committee,  
Comments on 21st Century Cures Initiative  
June 13, 2014

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### **Director of NIH and FDA Commissioner say...**

“[P]utting in place an appropriate risk-based regulatory framework is now critical to ensure the validation and quality of tests (called laboratory-developed tests, or LDTs) developed in-house by clinical laboratories.”

*New England Journal of Medicine* Perspective First FDA Authorization for Next-Generation Sequencer  
by National Institutes of Health Director Francis Collins, MD, PhD,  
and Food and Drug Administration Commissioner Margaret Hamburg, MD  
December 19, 2013

### **Food and Drug Administration says...**

“The increasing reliance on diagnostic tests in clinical decision making, combined with the dramatic shift in the number and complexity of LDTs being offered, are posing increasing risks to patients. FDA has been made aware of a number of examples where clinical decisions made on the basis of faulty tests resulted in harm to patients. As a result, FDA has been developing a risk-based framework for regulatory oversight of LDTs that would assure that tests, regardless of the manufacturer, have the proper levels of control to provide a reasonable assurance of safety and effectiveness, while also fostering innovation and progress in personalized medicine.”

FDA Report: Paving the Way for Personalized Medicine FDA  
October 2013

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### **Centers for Medicare and Medicaid Services says...**

“CLIA and its implementing regulations do not affect FDA’s authority under the FDCA to regulate LDTs or other devices used by laboratories.”

“CMS’ CLIA program does not address the clinical validity of any test — that is, the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient. On the other hand, FDA evaluates the clinical validity of a test under its premarket clearance and approval processes and as a result, has expertise in this area. In other words, the FDCA encompasses clinical validity whereas CLIA does not.”

CMS CLIA Overview and LDT Frequently Asked Questions  
October 22, 2013

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### **Members of Congress say...**

“We have reached a critical point in the development of advanced diagnostics at which it has become essential that FDA move this guidance forward to ensure appropriate and efficient oversight of safe and effective diagnostics.”

“The field of diagnostics has changed fundamentally and rapidly in recent years. A new generation of advanced molecular diagnostics — widely developed as LDTs — is increasingly determinative of critical treatment decisions for patients with life-threatening conditions. These advanced diagnostics, the cornerstone of personalized medicine, provide unprecedented insights into the presence and course of diseases and other health conditions.”

Joint Letter from Members of Congress to the Office of Management and Budget  
August 9, 2013

### **The New York Times says...**

“If a diagnostic test is made by a traditional device manufacturer, the Food and Drug Administration reviews its safety and effectiveness before approving it for marketing. However, if a test is developed by a clinical laboratory for use at its own facilities, it can be sold without a premarket review.”

“That bifurcated approach made sense in years past when a medical center might develop a diagnostic test for its own doctors and patients. But the landscape has changed with the advent of more sophisticated tests and the rapid expansion of commercial laboratory companies. Experts are unsure about how well these so-called laboratory-developed tests, or L.D.T.’s, perform in identifying diseases.”

“Regulations are long overdue; the draft guidelines should be quickly released for public comment.”

*New York Times* Editorial: The Gap in Medical Testing  
July 7, 2013

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### **FDA Commissioner says...**

“LDT’s have become more sophisticated and complex. Results from these tests are rapidly becoming a staple of medical decision-making, particularly for cancer. But relying on advanced diagnostics to make critical, life-altering treatment decisions exposes patients to obvious risks if these tests do not perform as expected. False results put patients at risk of a missed diagnosis or a wrong diagnosis that could result in either inappropriate treat or no treatment at all. The Agency is working to make sure that the accuracy and clinical validity of high-risk tests are established before they come to market.”

FDA Commissioner Margaret A. Hamburg, MD  
Address at the American Society of Clinical Oncology Annual Meeting, Chicago  
June 2, 2013

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### **Cancer Leadership Council says...**

“Over the years the number, complexity, and impact on health care decisions of LDTs have increased, and the differences between FDA-reviewed tests and LDTs have become less clear. In addition, cancer patients have in recent years suffered harm from LDTs that did not provide the accurate and meaningful information that was promised... The draft guidance on [FDA standards for evaluation of LDTs] should be published for public comment and advice without further delay.”

Letter to the Obama Administration  
November 21, 2012

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### **Patient Advocates say...**

“The widespread development and use of a new generation of advanced molecular diagnostics by clinical laboratories without FDA oversight has exposed a significant gap in the regulatory system. We believe the time has come for the Administration to address this regulatory gap and resolve the uncertainty hanging over this critical area of medicine by affirming FDA’s oversight of diagnostics.”

Letter to the Obama Administration  
November 14, 2012

### **American Heart Association says...**

“Because of the moderate-to-high complexity of many newer tests and their interpretation, testing requires the regulatory oversight by an authority capable of fully evaluating both the analytic validity and, especially, the clinical validity. As observed by the American Heart Association, the FDA is ideally suited to perform this function, because it has the clear statutory authority, scientific expertise, and experience in regulating genetic tests. It would be essential that the agency be appropriately resourced to ensure efficient test review and continued access to tests with established clinical validity.”

Genetics and Cardiovascular Disease, A Policy Statement From the American Heart Association  
July 3, 2012

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### **United Healthcare says...**

“Patients and their physicians need to be able to be confident that diagnostic tests are accurate and are both analytically and clinically valid. The current regulatory infrastructure for genetic tests and molecular diagnostics — which is primarily housed at the FDA and CMS — has important gaps. Current approaches focus on the quality of the testing process at laboratories, rather than evaluating the attributes of an individual test, leaving questions about test quality. Approaches also focus on the safety and efficacy of a subset of tests developed by manufacturers; however, there is minimal oversight of tests developed by laboratories (LDTs), leading to questions of the clinical validity of some tests. Furthermore, there are over 1,000 genetic disorders where tests are developed in labs and are not subject to FDA safety and effectiveness review.”

“Personalized Medicine: Trends and Prospects for the  
New Science of Genetic Testing and Molecular Diagnostics,” March 2012

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### **Ovarian Cancer National Alliance says...**

“The difference between a CLIA regulated test and an FDA regulated test is akin to restaurant reviews — CLIA is like a health inspection telling you that the restaurant is clean where FDA is like Zagat telling you the food is good.”

“A lower risk test, such as one for predicting baldness, might be regulated by FDA, but a high risk LDT, such as an ovarian cancer diagnostic test, might not be. Clearly, the likely medical interventions doctors would make, and the impact on patients would be very different for these two tests.”

*The Teal Journal*: “Laboratory Developed Tests: What Goes Wrong”  
September 2010

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### **National Health Council says...**

“The National Health Council (NHC) supports the FDA’s decision to reconsider its policy of enforcement discretion over LDTs. Diagnostic tests play a critical role in informing treatment planning for people with chronic disease. The NHC seeks to ensure that all diagnostic tests, including LDTs, undergo an appropriate level of scientific and regulatory oversight.”

August 15, 2010+

### **National Coalition for Cancer Survivorship says...**

“The National Coalition for Cancer Survivorship (NCCS) strongly supports the recent initiative by the Food and Drug Administration (FDA) to assert regulatory authority over laboratory-developed tests (LDTs). Our interest in this issue stems from concerns about the lack of reliable oversight of LDTs, which are increasingly important in identifying genetic or other anomalies that are the targets of new pharmaceutical or immunological interventions.”

August 11, 2010+

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### **Director of FDA’s Center for Devices and Radiological Health Director says...**

“FDA has observed the following problems with some LDTs in recent years:

- Faulty data analysis
- Exaggerated clinical claims
- Fraudulent data
- Lack of traceability/change control
- Poor clinical study design
- Unacceptable clinical performance”

Jeffrey Shuren, MD, Director, Center for Devices and Radiological Health, Food and Drug Administration  
Testimony to the House Energy and Commerce Committee Subcommittee on Oversight  
and Investigation Direct-to-Consumer Genetic Testing and the Consequences to the Public  
July 22, 2010

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### **The Institute of Medicine’s Evolution of Translational Omics Report says...**

“Lack of FDA oversight places an often unrecognized demand on academic institutions to provide proper oversight for omics-based test development, validation, and clinical use.”

*Evolution of Translational Omics — Report Brief*

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### **National Human Genome Research Institute says...**

“As the science of genomics advances, genetic testing is becoming more commonplace in the clinic. Yet most genetic tests are not regulated, meaning that they go to market without any independent analysis to verify the claims of the seller. The Food and Drug Administration (FDA) has the authority to regulate genetic tests, but it has to date only regulated the relatively small number of genetic tests sold to laboratories as kits. Whereas the Centers for Medicare and Medicaid Services (CMS) does regulate clinical laboratories, it does not examine whether the tests performed are clinically meaningful. Since the 1990s, expert panels and members of Congress have expressed concern about this regulatory gap and the need for FDA to address it.”

National Human Genome Research Institute

***The Secretary's Advisory Committee on Genetics, Health, and Society Report on U.S. System of Oversight of Genetic Testing says...***

“The Food and Drug Administration (FDA) should address all laboratory tests, regardless of how they are produced (i.e., as a commercial test kit or laboratory-developed test).”

“The Committee is concerned by the gap in oversight related to clinical validity and believes that it is imperative to close this gap as expeditiously as possible.”

“U.S. System of Oversight of Genetic Testing,” April 2008

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+2010 references are to comments made in connection with the U.S. Food and Drug Administration's July 19–20, 2010 public meeting, and the associated docket for public comments, regarding Oversight of Laboratory Developed Tests. Docket Number FDA-2010-N-0274.